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Previews

A Trip to Inner Space: Insights into Salt Balance from Cosmonauts

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The epidemiological association between high salt intake and hypertension is well established. However, in most patients, the specific defect causing salt-dependent hypertension cannot be discerned. In this issue of *Cell Metabolism*, Rakova and associates use an unprecedented study design to characterize long-term salt balance in humans (Rakova et al., 2012).

Sodium is the major cation in the extracellular fluid compartment, playing a key role in determining the extracellular fluid volume. Successful adaptation to extreme changes of sodium in the diet provides critical protection against fluid volume depletion or overload during extended exposure to low or high sodium intake, respectively. Impaired function of these homeostatic mechanisms may result in sodium sensitivity, characterized by marked fluctuation in blood pressure during rapid transitions between low and high salt intake (Kawasaki et al., 1978). Sodium sensitivity is a well-recognized precursor to hypertension (Weinberger et al., 1986) and may have a major impact when levels of dietary sodium intake are chronically elevated (He and MacGregor, 2011). Because of the virtually infinite capacity of the kidney to excrete excess sodium, it has been suggested that regulation of sodium excretion by the kidney may be a critical pathway for controlling fluid status, determining the level of intra-arterial pressure and mitigating sodium sensitivity (Coffman and Crowley, 2008; Guyton, 1991).

In the current issue, Rakova et al. (2012) describe unique, long-term experiments evaluating physiological responses to incremental changes in sodium intake in Russian cosmonauts, ensconced in the highly controlled environment of a space travel simulation training program called Mars500. The subjects were confined to an enclosed, restricted environment where they were provided diets with scrupulously defined sodium content while undergoing continuous monitoring of a range of parameters including urinary sodium excretion, blood pressure, body weight, and steroid hormone levels. These studies are remarkable for their sustained duration and tight control of environmental variables. As such, they provide a unique and detailed profile of the characteristics of long-term sodium balance in humans.

Current understanding of salt homeostasis in humans comes from a series of studies carried out over the past century, most of which were of short duration, evaluating responses to abrupt changes in salt intake over periods of days to weeks (Kawasaki et al., 1978). In normal subjects exposed to such challenges, balance between sodium intake and excretion is typically achieved within about 24 hr. In the first instance, the findings of Rakova et al. are consistent with this previous work. Over the short term, they find that abrupt increases of salt intake cause expansion of total-body sodium and extracellular water, with brisk suppression of aldosterone, a key hormone involved in regulating sodium excretion by the kidney, and consequent increase in urinary sodium excretion. On the other hand, they unexpectedly found that, relative to aldosterone, levels of two other key steroid hormones, cortisol and cortisone, moved in the opposite direction, increasing with high dietary salt and falling with reduced salt.

Despite the fixed sodium content in the diet, over time there was considerable day-to-day variability in 24 hr urinary sodium excretion, accompanied by fluctuations in excretion of aldosterone, cortisol, and cortisone. The authors examined these fluctuations with power spectral analysis, which demonstrated a regular pattern, peaking with a period interval of about 6 days. Regular fluctuations of total body sodium (TBNa), estimated using bioimpedance spectroscopy, were also observed, but with longer periodicity of approximately one month. The changes in total body sodium were positively correlated with aldosterone and negatively correlated with cortisol and cortisone, but independent of sodium intake and blood pressure. Since the study participants were largely insulated from the outside world, these patterns may reflect endogenous rhythms triggered by neuro-hormonal systems. One potential explanation for the uncoupling of changes in TBNa from body weight and blood pressure has been suggested by previous studies from these authors indicating that sodium can be stored without accumulation of water in the subdermal interstitium at hypertonic concentrations through interactions with proteoglycans (Machnik et al., 2009).

Along with the endogenous rhythms of sodium balance, the authors also observed physiological alterations associated with sleep deprivation. One of the simulation exercises, Mars105, included a night shift every 6th day. Among the group of Mars105 participants, blood pressure and urinary aldosterone excretion were consistently elevated on the day following night shift duty. Cardiovascular impact of sleep deprivation in humans has been reported previously

(Kato et al., 2000). Furthermore, this finding is reminiscent of mouse studies where disruption of the clock gene *Cry* is associated with hypertension caused by chronically enhanced aldosterone production by the adrenal gland (Doi et al., 2010).

In the cosmonaut trainees, blood pressures closely followed the content of sodium in the diet. Lower blood pressure levels were observed on the low-sodium diet (6 g/day), while blood pressures increased when dietary intake of sodium was increased 2-fold to 12 g/day. The changes in blood pressure lagged behind the early changes in body weight and the indirect measurements of extracellular water (ECW) and TBNa; with additional time on the high-salt diet, body weight, ECW, and TBNa decreased. One possible explanation of this seeming dissociation of blood pressure from ECW and TBNa comes from Guyton's predictions that volume expansion triggers autoregulatory responses, which will have the effect of reducing extracellular fluid volumes without changing blood pressure (Guyton, 1991). Admittedly, this has been difficult to prove directly, and it is possible that the dissociation of blood pressure from fluid volumes may also reflect complexities of sodium handling (Machnik et al., 2009) not accounted for by Guyton's hypothesis.

The human studies by Rakova et al. are unique, and it is unlikely that a study with this scope, duration, and level of environmental control will ever be repeated. As such, this represents an exceedingly valuable data set. However, there are some limitations that should be acknowledged. While there is unprecedented control of diet and environment in these studies, it remains possible that over the very long study period factors such as stress, compliance with diets, differences in physical exertion, and changes in lean body mass could confound the physiological assessments and their interpretations. Moreover, the measurements of ECW and TBNa are indirect and derivative. In addition, the subjects in the study are all males, and it is possible and even likely that characteristics of salt balance may differ in females (Sandberg and Ji, 2012). Finally, the relationships between changes in hormone levels and modifications of blood pressure, ECW, and TBNa are correlative. Thus, whether these hormones have a functional impact on the observed physiological outcomes cannot be determined from this work. Nonetheless, these correlations could be directly tested. For example, do corticosteroids affect excretion or internal disposition of sodium excretion? In this regard, the authors have previously shown that macrophages may regulate intradermal storage of sodium (Machnik et al., 2009), and corticosteroids have well-recognized actions to modulate inflammatory cells including macrophages. Another major question raised by this work is what systems determine the periodic fluctuations in sodium excretion and its regulators, and what is their contribution, if any, to sodium homeostasis and blood pressure control?

This trip to "inner space" has highlighted additional complexity in the mechanisms of salt balance in humans that cannot be easily explained by previous models. One hopes that further exploration of these findings will lead to better understanding of how high levels of salt in the diet lead to hypertension.

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